

The Examiner's several concerns are seen to be factual in nature. Therefore, facts are being submitted in response, in the form of Professor Wangh's declaration.

In paragraphs 3-5 and 13, Professor Wangh addresses the state of cloning prior to his invention. The facts discussed there are seen to address the Examiner's concern about the propriety of utilizing the Jepson format in this instance. Based on the facts presented, use of that format is seen to be appropriate. The steps of nuclear transfer were known: isolating nuclei, insertion of nuclei into recipient eggs by mechanical insertion or fusion, enucleation of recipient eggs, and activation had been worked out by others and published in the literature. Dr. Wangh did not invent these steps. What was missing, and what is the contribution of Dr. Wangh's invention, was to modify the cloning procedure to make it work with somatic cells by inserting into the procedure the critical step of reprogramming the nucleus. This is the very place for use of the Jepson format. Reconsideration and withdrawal of the rejection under 35 U.S.C. Section 112, paragraph 2, is requested.

The Examiner will note that in discussing the state of the art Dr. Wangh makes repeated reference to the Di Berardino book, portions of which are attached to his declaration. Applicant's attorney has obtained a copy of the book. The Examiner may wish to peruse the entire book. It is not known whether the book is available to the Examiner. However, because it is hard-bound, Applicant's attorney is reluctant to submit the book in the normal fashion. If the Examiner will telephone Applicant's attorney when she is ready to take up this case, Applicant's attorney will arrange to have his copy hand-delivered to the Examiner promptly for the Examiner's use and for inclusion as part of the record in this case.

The fact that, except for the missing reprogramming, the steps of nuclear transplantation and cloning had been worked out by others is also pertinent to enablement under the first paragraph of 35 U.S.C. Section 112. That which is novel must be taught by the specification, as the Examiner pointed out on page 8 of the Official Action. Conversely, that which was known does not have to be recounted in detail. Therefore, the enablement issue here is seen to relate to the novel steps this invention adds to the known cloning procedure.

Reprogramming occurs in the step of claim 87, namely, incubating the nucleus in unactivated egg cytoplasm before incubating in activated egg cytoplasm. Does that work, does it permit cloning of whole animals? The answer is a resounding yes. Commercial ventures and

academic laboratories around the world have utilized Dr. Wang's reprogramming successfully and have praised it as the key to success. Wilmut, the cloner of "Dolly", has publicly ascribed success to Dr. Wang's reprogramming, terming it "vital" to achieving a live birth. There is a BBC documentary, "Dawn of the Cloning Age," in which Wilmut discusses the reprogramming step, a substantial testimonial to Dr. Wang's invention. Applicant's attorney has obtained a videotape of the documentary and would like to submit it to the Examiner along with the Di Berardino book, if the Examiner will please telephone when she picks up this case.

Since publication of Dr. Wang's paper in 1995, cloning animals from somatic cell nuclei has literally "taken off." Reports of clones of commercially important species - - sheep, cows, pigs, as well as species important for numerous research purposes - - mice, are coming from all over the world. Dr. Wang reviews quite a number of these reports in paragraphs 14-21 of his declaration, where he shows that workers in the art have adopted the claimed method with great success. It works, and, as taught in the instant application, it is general.

On the issue of enablement, Dr. Wang was requested to address the novel step of claim 87, which is seen to be the Examiner's concern. Dr. Wang was also requested to address the step of dependent claim 111, on the chance that the Examiner might have a concern in that regard that would have to be addressed later. With respect to the novel step of claim 87, see paragraphs 9-10 of the Wang declaration. The facts are that the specification teaches that one begins with non-dividing nuclei, incubates them in unactivated egg cytoplasm (which may be an extract often referred to in the specification as "CSF extract") until chromosome-like structures appear, before incubating in activated egg cytoplasm. The instant specification teaches this critical step not only at the level of manipulation, but at the biochemical level. For example, the specification teaches that the cytoplasm contains high levels of mitosis promoting factor (MPF) and cytostatic factor (CSF), as well as histone H1 kinase activity. This biochemistry is presented at pages 34-39 of the application. \*

With respect to the cell cycle of the recipient egg, which the Examiner raised at page 8 of the Official Action, the teaching is seen to be definite. First of all, and most importantly, the specification teaches incubating in unactivated egg cytoplasm to permit chromosome-like

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\* In his declaration Dr. Wang cites to this portion of the specification as it appears in already issued patent 5,480,772.

structures to appear. Naturally, if one is using a recipient egg's cytoplasm for this purpose, as Dr. Wangh explains, persons skilled in the art would have understood from the application's teachings that the recipient egg's cytoplasm must have high CSF, high MPF and so forth. (Wangh declaration, paragraph 13). This teaches persons skilled in the art that the recipient egg cannot have reached the S-phase of the cell cycle - - it must be unactivated or just activated to have the required biochemistry. As the Examiner will note, most workers in the art have adopted the straightforward procedure of transferring into recipient eggs that are unactivated, which ensures that the S-phase cannot possibly have been reached. Further, at pages 59-60, the specification specifically states that transplantation can be carried out by "standard techniques" and cites two publications, one by Gurdon and one by King. As Dr. Wangh explains, the standard techniques were to transfer into a recipient egg prior to its entering the S-phase of the cell cycle. Thus, the specification teaches the status of the recipient egg in two ways.

As the Examiner is not seen to have raised a concern about enablement as to claim 111, the Examiner is referred to paragraphs 11-12 of Dr. Wangh's declaration as to that procedure.

#### CONCLUSION

Reprogramming is, in hindsight, not obtuse in concept and not difficult to practice. It is an incubation step performed on a prepared non-dividing cell nucleus prior to the traditional incubation in the cytoplasm of an activated egg. What the cytoplasm must be is taught at the biochemical level. The obvious place to find it, unactivated eggs, is taught as well. By adding this invention to known cloning procedures, diverse workers in the art around the world have cloned and are cloning commercial important animal species, particularly cows, pigs and sheep. Based on the facts now made of record, allowance of the pending claims is respectfully requested.

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Serial No. : 09/226,766  
Filed : January 6, 1999  
Page : 5

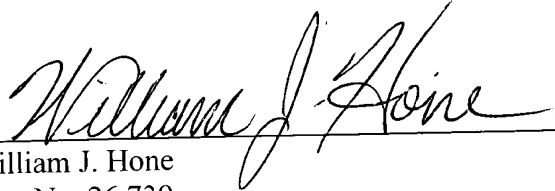
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Filed herewith is a check in payment of the Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: \_\_\_\_\_

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